PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	10/644,221
Filing Date	August 19, 2003
First Named Inventor	Hitoshi Nagaoka
Art Unit	1651
Examiner Name	Irene Marx
Attorney Docket Number	1217-031377

ENCLOSURES *(check all that apply)*

- [X] Fee Transmittal Form
  - [X] Fee Attached
- [ ] Amendment / Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts Under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [X] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Other Enclosure(s) (please identify below):

Checks for $250.00 (Appeal Brief filing fee); and return receipt postcard.

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	The Webb Law Firm		
Signature			
Printed Name	Barbara E. Johnson		
Date	June 19, 2007	Reg. No.	31,198

CERTIFICATE OF TRANSMISSION / MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: MAIL STOP APPEAL BRIEF - PATENTS, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	Florence P Trevethan		
Typed or printed name	Florence P. Trevethan	Date	June 19, 2007

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL For FY 2006

[X] Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 250.00

Complete if Known	
Application Number	10/644,221
Filing Date	August 19, 2003
First Named Inventor	Hitoshi Nagaoka
Examiner Name	Irene Marx
Art Unit	1651
Attorney Docket No.	1217-031377

METHOD OF PAYMENT (check all that apply)

[X] Check [ ] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 23-0650 Deposit Account Name: The Webb Law Firm

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

[ ] Charge fee(s) indicated below
[ ] Charge fee(s) indicated below, **except for the filing fee**
[X] Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17
[X] Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION (All the fees below are due upon filing or may be subject to a surcharge.)

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims	Fee ($)		Fee Paid ($)
_____	- 20 or HP =	_____	x _____	=	_____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)		Fee Paid ($)
_____	- 3 or HP =	_____	x _____	=	_____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____	(round up to a whole number) x	_____	=	_____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Appellant's Brief ($250.00 fee).	$250.00

SUBMITTED BY

Signature	Barbara E. Johnson	Registration No. (Attorney/Agent) 31,198	Telephone 412-471-8815
Name (Print/Type)	Barbara E. Johnson		Date June 19, 2007

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NO SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application No.	:	10/644,221			
Appellant	:	Hitoshi Nagaoka			
Filed	:	August 19, 2003			
Title	:	INHIBITOR OF HEPATITIS B AND HIV ACTIVITY			
Group Art Unit	:	1651	Confirmation No.	:	6470
Examiner	:	Irene Marx	Customer No.	:	28289

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF UNDER 37 C.F.R. §41.37

Sir:

This Appeal Brief is submitted in support of the Notice of Appeal filed April 16, 2007.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to MAIL STOP APPEAL BRIEF – PATENTS, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on June 19, 2007.

Florence P. Trevethan
(Name of Person Mailing Paper)

Florence P. Trevethan 06/19/2007
Signature Date

J89420

The headings used hereinafter and that which is set forth under each heading are in accordance with 37 C.F.R. §41.37(c).

I. REAL PARTY IN INTEREST

The real party in interest is Hitoshi Nagaoka.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to Appellant or Appellant's legal representative which will directly affect, or be directly affected by or have a bearing on a decision in the present Appeal.

III. STATUS OF CLAIMS

Claims 1-2 are pending in the present application and are the subject of this appeal. Claims 3-5 have been canceled and are not at issue in this Appeal.

Claims 1-2 stand finally rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

Claims 1-2 stand finally rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

IV. STATUS OF AMENDMENTS

There are no unentered amendments to the claims of this application. A copy of the claims involved in this Appeal in their current form is contained in the Claims Appendix attached hereto.

V. SUMMARY OF CLAIMED INVENTION

A representative embodiment of the Appellant's invention is set forth in independent claim 1 of this application. The *Lentinus edodes* is inoculated in a solid culture medium comprising 90 parts by weight of bagasse and 10 parts by weight of rice bran to yield proliferated mycelium, as described in

Claim 1, section (a). The solid culture medium containing the proliferated mycelium is then disentangled so that the amount of the bagasse of 12-in mesh is not more than 30% by weight, followed by adding thereto 1 to 10 kg of water and 0.5 to 5 g of at least one enzyme selected from the group consisting of cellulase, protease and glucosidase based on 1 kg of the disentangled solid culture medium, while keeping the solid culture medium at 30 to 50°C, to give a bagasse-containing mixture (Claim 1, section (b)). Next, the bagasse-containing mixture is ground and milled so that the amount of the bagasse of 12-in mesh is not less than 70% by weight, and the ground and milled bagasse-containing mixture is then heated to a temperature of 75 to 95°C to inactivate the enzyme (Claim 1, sections (c)-(d)). The resultant mixture is then filtered through a filter cloth of 50 to 120-in mesh to obtain thereby a purified, concentrated pharmaceutical *Lentinus edodes* mycelium extract (Claim 1, section (e)). Finally, the at least one effective dose of the purified concentrated extract is administered orally to a human, and the extract weakens HIV activity and inhibits HIV proliferation in said human (Claim 1, section (f)).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claim 1 is indefinite under 35 U.S.C. §112, ¶2, for failing to particularly point out and distinctly claim whether "at least one effective dose" weakens HIV activity and inhibits HIV proliferation in said human, and what that effective dose is.

B. Whether the specification provides enablement under U.S.C. §112, ¶1, for the method of treating a human infected with HIV by orally administering at least one effective dose according to claims 1-2.

VII. ARGUMENT

A. *CLAIM 1 DISTINCTLY CLAIMS "AT LEAST ONE EFFECTIVE DOSE" AND THEREFORE AVOIDS INDEFINITENESS UNDER 35 U.S.C. §112, ¶2.*

Claims 1-2 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

a. *CLAIM 1 IS NOT VAGUE, INDEFINITE AND CONFUSING IN LACKING CLEAR ANTECEDENT BASIS FOR "SAID PURIFIED, CONCENTRATED EXTRACT" OR FOR "SAID EXTRACT" AT LINES 1-2 of (f).*

Claim 1 is not vague, indefinite and confusing in lacking clear antecedent basis for said "purified, concentrated extract" at lines 1-2 of (f) or for "said extract" at line 2 of (f). A lack of antecedent basis arises where the claim contains no earlier recitation or limitation or where it would be unclear as to what element the limitation was making reference. This is not the case in Claim 1.

Claim 1, as seen in the Claims Appendix, reflects the additions and deletions incorporated by the last entered Amendment dated July 13, 2006. In section (e) of Claim 1, the extract is introduced as a purified, concentrated pharmaceutical *Lentinus edodes* mycelium extract. In lines 1-2 of section (f) of Claim 1, Appellant correctly refers to the purified, concentrated pharmaceutical *Lentinus edodes* mycelium extract as "said extract." Because the claim contains an earlier recitation or limitation and it is clear as to what element the limitation was making reference, Claim 1 is not vague, indefinite and confusing in lacking clear antecedent basis.

b. THE CLAIM IS NOT AMBIGUOUS AS TO WHETHER THE AT LEAST ONE EFFECTIVE DOSE WEAKENS HIV ACTIVITY AND INHIBITS HIV PROLIFERATION IN SAID HUMAN.

In reviewing a claim for compliance with 35 U.S.C. §112, second paragraph, the Examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. §112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). In the present application, the *Lentinus edodes* infusion was previously known, as described in the specification at paragraph 7. The infusion was already known as a healthy drink and the amount and route of administration for the composition of the present invention was already known and appreciated in the prior art. Because the essence of the present invention is not in the preparation and general administration of the *Lentinus edodes* infusion, but, rather, the new and unexpected identification of the medical indications, notably, anti-HIV, the administration of the *Lentinus edodes* infusion has an indication-specific medicinal effect even when given according to prior art dosages and routes of administration.

To those skilled in the art, particularly those skilled in the art of the prior art of *Lentinus edodes* infusion, the effective dose is apparent from the present specification. The present specification gives very particular direction as to how to prepare the *Lentinus edodes* infusion (specification at paragraphs 20-28). The composition thus made is administered in beverage amounts, which, as a practical matter, involve a few to several ounces per administration, and such administration is described, for example at specification paragraphs 28-30. The "appropriate diluting" discussed in the specification does not refer to dosage

adjustment, but as in the case of other healthy drink type preparations, the claimed infusion can be diluted, or not, prior to consumption.

Because the "at least one effective dose" is not ambiguous to one of ordinary skill in the art, the rejection of claims 1-2 under 35 U.S.C. §112, ¶2, should be reversed.

B. THE APPLICATION AS ORIGINALLY FILED SUFFICIENTLY ENABLES THE INVENTION WITH RESPECT TO THE CLAIMED ONE EFFECTIVE DOSE TO SATISFY THE ENABLEMENT REQUIREMENT UNDER 35 U.S.C. §112, ¶1

Claims 1-2 are rejected under 35 U.S.C. §112, ¶1, for allegedly failing to comply with the enablement requirement. Claim 1 recites "administering orally at least one effective dose." The Office Action alleges that the specification, as originally filed, fails to provide enablement for such an effective dose. In particular, the Office Action contends that the claims are broadly drawn to a method of treating a human infected with HIV by orally administering at least one effective dose, without amounts and concentrations, and that the intended effect of this dose is not clearly delineated.

A specification is enabling if it teaches those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). It is not necessary that the specification describe how to make every variant of the claimed invention because the artisan's knowledge of the prior art and routine experimentation can fill in the gaps. *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003).

a. ONE EFFECTIVE DOSE IS APPARENT FROM THE INSTANT WRITTEN DISCLOSURE.

Because "one effective dose" is apparent in the instant written disclosure, claims 1-2 are enabled under 35 U.S.C. §112, ¶1. The *Lentinus edodes* infusion of the present application was previously known, as described in

the specification at paragraph 7. Because the infusion was already known as a healthy drink, the amount and route of administration for the composition of the present invention was already known and appreciated in the prior art. The essence of the present invention is not primarily in the preparation and general administration of the *Lentinus edodes* infusion, therefore, but emphasizes the infusion's new and unexpected effectiveness against HIV, such that administration of the *Lentinus edodes* infusion has an indication-specific medicinal effect even when given according to prior art dosages and routes of administration. In this instance, it is precisely the artisan's knowledge of the prior art, according to *AK Stell Corp. v. Sollac and Ugine*, that makes one skilled in the art realize that the effective dose is a "healthy drink" dose, or a beverage amount dose. Appellant asks the Board to recognize that such a dose amount, a beverage dose, is a typical effective dose in herbal pharmaceutical practice both in history and throughout the world today.

In a prior decision by the CCPA, the Appellant had claimed the method of using certain compounds to produce antidepressant activity. *In re Garner*, 427 F.2d 786, 166 USPQ 138 (CCPA 1970). In the specification, there was not a single specific example or embodiment by way of an illustration of how the invention was supposed to be practiced on any kind of host. *Id.* at 789. The specification did not disclose whether the contemplated "host" of the compound was human or an animal or what the proper dosage should be. *Id.* The Court of Customs and Patent Appeals held that the specification required an unreasonable amount of experimentation on the part of a person skilled in the art. *Id.*

The present facts are unlike those of Garner. The present application discloses treating a human with a healthy drink, or beverage dose, to treat HIV, and also presents positive *in vitro* test results using *Lentinus edodes* to treat human MT-4 cells infected with HIV. In other words, in distinction to Garner, not only are the host (human), route of administration (oral), and

effective dose(s) all apparent from the specification, corroborating *in vitro* evidence of the claimed medicinal indication is also provided in the specification (Table 1). Those skilled in the art thus are made aware of how to make the present mycelium infusion, how to administer it, and to whom, and what the medical benefit will be. In addition, analogous *in vivo* tests showing efficacy of the same drink in the same amount against Hep-B is also of record (Sawadaishi Declaration signed February 28, 2003).

b. THE PREPARATION OF LENTINUS EDODES FOR THE PURPOSE OF TREATING HIV INFECTIONS IS ENABLED UNDER 35 U.S.C. §112, ¶1, BY THE ORIGINALLY FILED SPECIFICATION.

The administration of *Lentinus edodes* is predictable for the purposes of practicing the claimed invention and, therefore, the present invention is enabled. All strains of *Lentinus edodes* may be used in the claimed invention, and, thus, there is no need to specify any particular *Lentinus edodes* strain. To corroborate this point, Appellant cites Expert's Declaration dated May 11, 1998, submitted and made part of the record in the parent Application No. 08/519,293. In the Declaration, the declarant attests, in paragraph 7, that "Any strain of the fungus Lentinus edodes is suitable for use in practicing the claimed invention," and "My prior Declaration [dated June 9, 1997] reported results achieved using one strain of Lentinus edodes, and that strain was is [sic] exemplary of all strains of Lentinus edodes. The anti-HIV efficacy of an extract produced according to the present invention is essentially unaffected by the strain of Lentinus edodes." (Sawadaishi Declaration May 11, 1998). Based on the foregoing, Appellant submits that the specification enables the preparation and administration of an anti-HIV *Lentinus edodes* mycelium extract of any *Lentinus edodes* strain.

c. THE IN VITRO TESTING CORRELATES WITH THE TREATMENT OF A HUMAN AS CLAIMED WITH AN "AT LEAST ONE EFFECTIVE DOSE" AND, THEREFORE, IS ENABLED UNDER 35 U.S.C. §112, ¶1.

The Office Action further asserts that the *in vitro* testing presented on the record fails to correlate with the treatment of a human as claimed with an "at least one effective dose".

Appellant presents an example of the treatment of human T4 lymph cells MT-4 cells infected with a particular strain of HIV (specification at paragraphs 35-51). The data of Table 1 shows the inhibition of HIV virus in MT-4 cells (specification at paragraph 49). When concentration of HIV activity inhibitor exceeds 125 μg/ml, the viability of the MT-4 cells is reduced because of the influence originating from the HIV activity inhibitor, even if the cells are not infected with HIV (specification at paragraph 51). However, in the concentrations of not higher than the above concentration, with increase of the concentration of the HIV activity inhibitor, the viability of the HIV-infected MT-4 cells increases owing to the anti-AIDS viral effect of the HIV activity inhibitor (specification at paragraph 51). In particular, when the concentration of the HIV activity inhibitor is 125 μg/ml, the viability of the HIV-infected MT-4 cells is 71.5% (specification at paragraph 51). The anti-HIV effect was measured in accordance with the method described in "Antiviral Research," Vol. 20, pp. 317-331, (1993) (specification at paragraph 42). These *in vitro* data were presented in the specification to corroborate the enablement of and to illustrate and thereby to correlate to, the effectiveness of the dosage regime and treatment method.

Correlation refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. MPEP 2164.02. If there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity based upon the relevant evidence as a whole, a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. *Cross v. Iizuka*, 753 F.2d 1040,

1050, 224 USPQ 739, 747 (Fed. Cir. 1985). In a manner analogous to the utility requirement of 35 U.S.C. § 101, a patent application is not required to show both *in vitro* and *in vivo* test results and the correlation between them, but is required only to establish a reasonable evidentiary showing supporting an asserted therapeutic effect (utility). MPEP 2107.03 The MT-4 results are in the specification for just this reason. When Appellant submitted the MT-4 results in the specification and urged such results as supportive of the asserted enablement, Appellant identified an effectiveness correlation with their enabled effective dose. The *in vitro* results in the Sawadaishi Declaration dated June 9, 1997 give further confirmation. Clinical test results corroborating and correlating anti-Hepatitis B results appear in the Sawadaishi Declaration dated February 28, 2003.

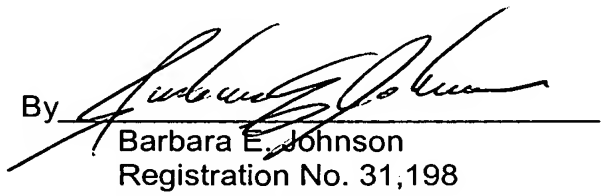
VIII. CONCLUSION

In view of the foregoing, it is respectfully submitted that the rejections of claims 1-2 under 35 U.S.C. §112, first paragraph, and the rejection of claims 1-2 under 35 U.S.C. §112, second paragraph, are improper, and that pending claims 1-2 are allowable. Appellant therefore respectfully urges the Board to reverse the Examiner's final rejections of the claims.

A check for $250.00 to cover the small entity fee for filing an Appeal Brief Under 37 C.F.R. §41.37 accompanies this Appeal Brief. The Commissioner for Patents and Trademarks is hereby authorized to charge any additional fees which may be required to Deposit Account No. 23-0650. Please refund any overpayment to Deposit Account No. 23-0650. An original and two copies of this Appeal Brief are enclosed.

Respectfully submitted,

THE WEBB LAW FIRM

By 

Barbara E. Johnson
Registration No. 31,198
Attorney for Appellant
700 Koppers Building
436 Seventh Avenue
Pittsburgh, Pennsylvania 15219
Telephone: 412-471-8815
Facsimile: 412-471-4094
E-mail: webblaw@webblaw.com

CLAIMS APPENDIX

Claim 1 (Previously presented): A method for treating a human infected with human immunodeficiency virus (HIV), comprising:

(a) inoculating *Lentinus edodes* fungus in a solid culture medium comprising 90 parts by weight of bagasse and 10 parts by weight of rice bran to yield proliferated mycelium;

(b) disentangling the solid culture medium containing the proliferated mycelium so that the amount of the bagasse of 12-in mesh is not more than 30% by weight and adding thereto 1 to 10 kg of water and 0.5 to 5 g of at least one enzyme selected from the group consisting of cellulase, protease and glucosidase based on 1 kg of the disentangled solid culture medium, while keeping the solid culture medium at 30 to 50°C, to give a bagasse-containing mixture;

(c) grinding and milling the bagasse-containing mixture so that the amount of the bagasse of 12-in mesh is not less than 70% by weight;

(d) heating the ground and milled bagasse-containing mixture to a temperature of 75 to 95°C to inactivate the enzyme;

(e) filtering the resultant mixture through a filter cloth of 50 to 120-in mesh to thereby obtain a purified, concentrated pharmaceutical *Lentinus edodes* mycelium extract; and

(f) administering orally at least one effective dose of said purified, concentrated extract to said human, wherein said extract weakens HIV activity and inhibits HIV proliferation in said human.

Claim 2 (Original): The method according to claim 1 wherein the enzyme is cellulase.

Claims 3-5 (Canceled).

EVIDENCE APPENDIX

Sawadaishi Declaration of June 9, 1997	Made of record by the Examiner during the prosecution of parent U.S. Patent Application 08/519,293
Sawadaishi Declaration of May 11, 1998	Made of record by the Examiner during the prosecution of parent U.S. Patent Application 08/519,293
Sawadaishi Declaration of February 28, 2003	Made of record by the Examiner during the prosecution of parent U.S. Patent Application 08/519,293

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group Art Unit 1808 :

In re application of :

HITOSHI NAGAOKA : INHIBITOR OF HEPATITIS B AND HIV ACTIVITY

Serial No. 08/519,293 :

Filed August 25, 1995 :

Examiner - I. Marx :

Pittsburgh, Pennsylvania

DECLARATION-2

Hon. Commissioner of Patents and Trademarks
Washington, D. C. 20231

Sir:

I, Hideo Sawadaishi, declare as follows:

1. I am a citizen of Japan, and residing at Sunny Homes Negishi B 101, Tsutsumidai 83, Noda-shi, Chiba-ken, Japan.

In March, 1975, I was graduated from a prefectural Shimizu Senior high school, Department of Industrial Chemistry.

Since April, 1975 till 1991, I have been an employee of Noda Shokkin Kogyou K.K., I was engaged in various research and development works in Lentinus edodes mycelium.

Since 1991, I have been an employee of NAGAOKA L.E.M. LABORATORY Co., LTD., and till the present time, I have been engaged in research and development works in various research and development works in Lentinus edodes mycelium.

2. I am familiar with the contents of the present invention as well

as of the prior art references cited in the official action.

3. In order to further support the unexpected results obtained from the extract of the present invention, I carried out the following Experiments I, II and III.

Experiment I

1 kg of solid culture medium (bagasse/rice bran : 9/1) was disentangled so that the amount of the bagasse fibers of 12-in mesh was 24 % by weight. To the disentangled solid culture medium were added 3.5 liters of purified water and 2 g of purified cellulase as an enzyme with keeping the solid culture medium at 37 ℃ for 1 hour, to give a bagasse-containing mixture.

Then, the mixture was further heated up to 70℃ and allowed to stand for 1 hour at the same temperature. By the heating, inactivation of the enzyme of the mixture was performed.

The resultant mixture was filtered through a filter cloth of about 100-mesh to obtain a filtrate. The thus obtained filtrate was subjected to lyophilization to obtain a powdery material (Sample 1).

With respect to Sample 1, the anti-Human Immunodeficiency Virus (HIV) effect was measured in the same manner as in Test Examples 1 to 10 of the Preparation Example 1. The results are shown in Table A.

Table A (Sample 1)

Test No.	Concentration (μ g/ml)	MT-4		MT-4/HIV	
		Absorbance	Viability (%)	Absorbance	Viability (%)
1	Control	1.058	100.0	0.093	8.8
2	3.9063	1.117	105.6	0.104	9.8
3	7.8125	1.130	106.8	0.108	10.2
4	15.6250	1.114	105.3	0.127	12.0
5	31.2500	1.138	107.6	0.134	12.7
6	62.5000	1.092	103.2	0.181	17.1
7	125.0000	0.964	91.1	0.266	25.1
8	250.0000	0.106	10.0	0.115	10.9
9	500.0000	0.026	2.5	0.030	2.8
10	1000.0000	0.023	2.2	0.026	2.5

Experiment II

A pharmaceutical Lentinus edodes mycelium extract for inhibiting human immunodeficiency virus activity (Sample 2) was prepared in the same manner as in Preparation Example 1 of the present specification except that the amount of the purified cellulase is changed to 0.5 g from 2.0 g.

With respect to Sample 2, the anti-Human Immunodeficiency Virus (HIV) effect was measured in the same manner as in Test Examples 1 to 10 of the Preparation Example 1. The results are shown in Table B.

Table B (Sample 2)

Test No.	Concentration (μ g/ml)	MT-4		MT-4/HIV	
		Absorbance	Viability (%)	Absorbance	Viability (%)
1	Control	1.168	100.0	0.095	8.1
2	3.9063	1.242	106.3	0.182	15.6
3	7.8125	1.289	110.4	0.196	16.8
4	15.6250	1.308	112.0	0.331	28.3
5	31.2500	1.303	111.6	0.334	28.6
6	62.5000	1.292	110.6	0.494	42.3
7	125.0000	1.149	98.4	0.712	70.0
8	250.0000	0.127	10.9	0.165	14.1
9	500.0000	0.031	2.7	0.057	4.9
10	1000.0000	0.023	2.0	0.043	3.7

Experiment III

A pharmaceutical Lentinus edodes mycelium extract for inhibiting human immunodeficiency virus activity (Sample 3) was prepared in the same manner as in Preparation Example 1 of the present specification except that the amount of the purified cellulase is changed to 5 g from 2.0 g.

With respect to Sample 3, the anti-Human Immunodeficiency Virus (HIV) effect was measured in the same manner as in Test Examples 1 to 10 of the Preparation Example 1. The results are shown in Table C.

Table C (Sample 3)

Test No.	Concentration (μ g/ml)	MT-4		MT-4/HIV	
		Absorbance	Viability (%)	Absorbance	Viability (%)
1	Control	1.146	100.0	0.091	7.9
2	3.9063	1.229	107.2	0.167	14.6
3	7.8125	1.269	110.5	0.187	16.3
4	15.6250	1.305	113.9	0.324	28.3
5	31.2500	1.303	113.7	0.339	29.6
6	62.5000	1.298	113.3	0.496	43.3
7	125.0000	1.149	100.3	0.618	70.8
8	250.0000	0.117	10.2	0.158	13.8
9	500.0000	0.049	4.3	0.050	4.4
10	1000.0000	0.044	3.8	0.037	3.2

From the results shown in Tables A, B and C, and based on may knowledge, I conclude that:

The results of the Experiment I show that when the concentration is 125μ g/ml, the viability of the HIV-infected MT-4 cells to Sample 1 is as low as 25.1.

By contrast, the results of the Experiments I and II show that when the concentration is 125 μ g/ml, the viabilities of the HIV-infected MT-4 cells to Samples 1 and 2 are as high as 70.0 and 70.8, respectively.

Thus, according to the present invention, such high viability of the HIV-infected MT-4 cells can be attained.

4. I declare further that all statements made herein of my own knowledge are true and that statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

this 9th day of June, 1997

澤田石 英雄

Hideo SAWADAISHI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group Art Unit 1808 :

In re Application of :

HITOSHI NAGAOKA : INHIBITOR OF HEPATITIS B AND HIV ACTIVITY

Serial No. 08/519,293 :

Filed August 25, 1995 :

Examiner - I. Marx :

DECLARATION-3

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Hideo Sawadaishi, declare as follows:

1. I am a citizen of Japan, and residing at Sunny Homes Negishi B 101, Tsutsumidai 83, Noda-shi, Chiba-ken, Japan. I graduated from prefectural Shimizu Senior High School, Department of Industrial Chemistry in March 1975. From April 1975 through 1991, I was an employee of Noda Shokkin Kogyou K.K. where I engaged in various research and development projects concerning Lentinus edcdes mycelium. Since 1991, I have been an employee of Nagaoka L.E.M. Laboratory Co., Ltd., and during this time, I have been engaged in research and development projects concerning Lentinus edodes mycelium.

2. I am familiar with the contents of the present invention as well as of the prior art references cited in the application.

3. My prior Declaration dated October 4, 1995, presents data comparing compositions prepared according to the method disclosed in Japanese Patent Publication No.

1-312980 to Iizuka et al. ("Iizuka '980") and prepared according to the presently claimed invention. The data set forth in Table C of the October 4, 1995 Declaration shows that the culture mixture produced according to Iizuka '980 (Experiment III) contained a low relative amount of protein (5.4%) and a high relative amount of fiber (25.1%). In contrast, the extract produced according to the claimed invention (Experiment IV) contained a high relative amount of protein (27.0%) and a low relative amount of fiber (0.07%). The dramatic differences between the culture mixture of Iizuka '980 and the extract of the present invention are due to the addition of water and enzymes and the filtering step performed in the practice of the claimed invention.

4. Iizuka '980 teaches use of a culture mixture containing fungus and bagasse as a healthy food. The purpose of the process disclosed in Iizuka '980 is to obtain a fibrous dietary product, hence the culture mixture has a high fiber content and low protein content.

5. The present invention relates to a filtrate of a fungal culture to which extraneous enzymes and water were added. The final step in the claimed method removes the fungus and solid culture medium leaving an extract which the applicant discovered possesses anti-HIV activity. These key process steps of (1) adding enzymes and (2) filtering the medium to obtain an extract are responsible for the high protein content and anti-HIV activity of the extract.

6. A composition produced according to Iizuka '980 would not be expected to have efficacy against HIV because it is produced by a significantly different type of process from the claimed invention. If the Iizuka '980 composition were added to a culture of HIV-infected cells in an amount comparable to the efficacious amount of the extract produced according to the claimed invention is added to cultures of HIV infected

cells, the viability of such cells treated with the Iizuka '980 composition would not be expected to improve. This is because the culture mixture of Iizuka '980 is not produced by adding extraneous enzymes or separation of the fluid portion thereof. The extraneous enzymes are believed to release components essential to anti-HIV activity from the fungus into the culture medium. Upon filtration, the resulting filtrate contains the anti-HIV components in an efficacious concentration. Without the addition of enzymes or separation to obtain a filtrate, the surprising anti-HIV activity disclosed in the present application would not have occurred.

7. Any strain of the fungus Lentinus edodes is suitable for use in practicing the claimed invention. My prior Declaration reported results achieved using one strain of Lentinus edodes, and that strain was is exemplary of all strains of Lentinus edodes. The anti-HIV efficacy of an extract produced according to the present invention is essentially unaffected by the strain of Lentinus edodes.

8. I declare further that all statements made herein of my own knowledge are true and that statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any patent issuing thereon.

澤田秀雄

Hideo Sawadaishi

Date May 11, 1998

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Group Art Unit 1651 :

In re Application of :

Hitoshi NAGAOKA : **INHIBITOR OF HEPATITIS B AND HIV ACTIVITY**

Serial No. 08/519,293 :

Filed August 25, 1995 :

Examiner - I. Marx :

Pittsburgh, Pennsylvania
February 27, 2003

DECLARATION

Commissioner of Patents
Washington, D.C. 20231

I, Hideo Sawadaishi, declare as follows:

1. I am a citizen of Japan, and reside at 1-20-2-103, Todaijima, Urayasu-shi, Chiba-ken, Japan. I graduated from prefectural Shimizu School, Department of Industrial Chemistry in March 1975. From April 1975 through 1991, I was an employee of Noda Shokkin Kogyou K.K. where I engaged in various research and development projects concerning Lentinus edodes mycelium. Since 1991, I have been engaged in research and development projects concerning Lentinus edodes mycelium.

2. I have read and am thoroughly familiar with the contents of the above-identified patent application as well as of the prior art references cited in the application. I have read and I understand new claim 20.

3. In order to support further the unexpected results obtained from the Lentinus edodes mycelium extract of the present invention, my colleagues Kijuroh Nomura and Hitoshi Nagaoka conducted a scientific investigation in order to determine the effectiveness of the extract in treating patients with hepatitis B virus. I followed the scientific investigation closely at the time it was completed and have personal knowledge that the attached twenty pages are a true and correct summary of tests conducted and results achieved. The contents and significance of the attachment is summarized briefly below.

Method

Fifty-eight patients having acute or chronic hepatitis B were given 2 g daily of an Lentinus edodes mycelium extract powder, prepared according to claim 20, in the form of a drink. In particular, the extract was prepared by inoculating *Lentinus edodes* fungus in a solid culture medium comprising 90 parts by weight of bagasse and 10 parts by weight of rice bran to yield proliferated mycelium; disentangling the solid culture medium containing the proliferated mycelium so that the amount of the bagasse of 12-in mesh is not more than 30% by weight and adding thereto 1 to 10 kg of water and 0.5 to 5 g of at least one enzyme selected from the group consisting of cellulase, protease and glucosidase based on 1 kg of the disentangled solid culture medium, while keeping the solid culture medium at 30 to 50 ° C, to give a bagasse-containing mixture; grinding and milling the bagasse-containing mixture so that the amount of the bagasse of 12-in mesh is not less than 70% by weight; heating the ground and milled bagasse-containing mixture to a temperature of 75 to 95° C to inactivate the enzyme; filtering the resultant mixture through a filter cloth of 50 to 120-in mesh to thereby obtain a pharmaceutical

Lentinus edodes mycelium extract; and administering at least one effective dose of said extract to an animal or human afflicted with a viral disease. The patients' response to treatment were evaluated by measuring serum levels of GOT and GPT enzymes as well as serum levels of hepatitis B "e" (Hbe) antigens and antibodies (a known marker for hepatitis B virus infection).

Results

There was a highly significant response to Lentinus edodes mycelium extract treatment. Seventy-two percent of the patients seroconverted from Hbe antigen positivity to Hbe negativity, and responded with a 50% or more reduction in their GOT and GPT serum liver enzymes. Of the 72% of the patients that responded favorably to treatment, 15.5% of the patients had GOT and GPT values of 40 units or less, and the remaining 56.9% had GOT and GPT values of 100 or less. These patients also reported an improvement in their subjective symptoms. None of the patients in the study reported having any adverse side effects from the treatment or any worsening of symptoms.

Conclusion

A highly significant percentage of patients infected with hepatitis B, after daily treatment with the Lentinus edodes mycelium extract of the present invention, showed a remarkable improvement in their serum liver enzymes, which was accompanied by Hbe seroconversion from positive to negative, a subjective improvement in symptomatology, and a complete lack of adverse side effects. I also know from my expertise in the area of hepatitis B that hepatitis B patients, left untreated, do not undergo Hbe seroconversion to a highly significant percentage. I therefore conclude that the results of this patient study emphasize that claim 20 (i.e., the above-described method of making an extract and

administering an effective amount to a patient in need of treatment for a viral disease) recites a way of treating viral diseases which accomplishes new and unexpectedly efficacious results, as compared to conventional treatment or no treatment.

4. I declare further that all statements made herein of my own knowledge are true and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any patent issuing thereon.

Hideo Sawadaishi

Hideo Sawadaishi

Date February 28, 2003